Efficacy of exercise for functional outcomes in older persons with dementia

Sanders, Lianne

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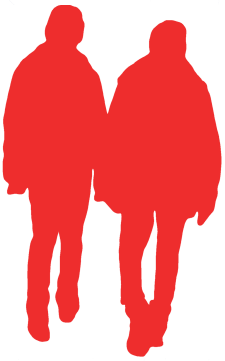
Chapter 4

Low- and high-intensity physical exercise has small effects on physical but not on cognitive function in older patients with dementia



A randomized controlled trial

L.M.J. Sanders, T. Hortobágyi, E.G.A. Karssemeijer, E.A. van der Zee, E.J.A. Scherder, M.J.G. van Heuvelen

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Abstract

Background

Potential moderators such as exercise intensity or apolipoprotein-E4 (ApoE4) carriership may determine the magnitude of exercise effects on physical and cognitive functions in patients with dementia (PwD). We determined the effects of a 24-week aerobic and strength training program with a low and high intensity phase on physical and cognitive function.

Methods

In an assessor-blinded randomized trial, 91 PwD (all-cause dementia, recruited from daycare and residential care facilities, age 82.3±7.0y, 59 women, Mini Mental State Examination 20.2±4.4) were allocated to the exercise or control group. In the exercise group PwD participated in a walking and lower-limb strength-training program with 12 weeks low and 12 weeks high intensity training offered three times/week. Attention-matched control participants performed flexibility exercises and recreational activities. We assessed adherence, compliance and exercise intensity for each session. We assessed physical (endurance, gait speed, mobility, balance, leg strength) and cognitive (verbal memory, visual memory, executive function, inhibitory control, psychomotor speed) function with performance-based tests at baseline and after 6, 12, 18, 24, and 36 (follow-up) weeks. ApoE4-carriership was determined post-intervention.

Results

69 PwD were analyzed. Their mean attendance was ~60% during the study period. There were consistently small but non-significant effects of the exercise vs. control intervention on endurance, mobility, balance and leg strength in favor of the exercise group. Gait speed significantly improved during the high intensity phase for exercise participants, but declined at follow-up. There were no significant effects of the exercise vs. control intervention on any of the cognitive measures. ApoE4 non-carriers in the exercise group improved on the MMSE after 24 weeks, whereas MMSE scores for all other participants declined (trend-level significance).

Conclusions

Exercise was superior to control activities for gait speed in our sample of PwD. However, the training effect provided no protection for mobility loss after detraining (follow-up). Exercise vs. control activities were not superior in slowing the rate of cognitive decline. Exercise intensity moderated the effects of exercise on gait speed. ApoE4-carriership moderated the effect of exercise on global cognition only (trend-level).

Trial registration

Nederlands Trial Register, NTR5035. Registered 2 March 2015, https://www.trialregister.nl/trial/4933.

Background

The number of patients with dementia (PwD) is growing from 50 million worldwide in 2017 to 80 million in 2030 [1]. Dementia is characterized by progressive neurodegeneration and severe functional losses. The clinical relevance of pharmacological treatments remains uncertain and the risk of adverse reactions is high [2]. Exercise may be a treatment alternative to drugs to slow functional declines in dementia. In healthy older adults, both aerobic and strength exercise are associated with improvements in cognitive functions such as executive function, inhibitory control and episodic memory [3-5] and physical functions, i.e., muscle strength, balance, functional reach, mobility and endurance [4, 6-9]. Regrettably, the effects of exercise on these cognitive and physical functions in PwD have been inconsistent [5, 10-14]. In PwD combined aerobic and strength exercise appears to be more effective for cognitive and physical benefits than aerobic training only [11].

Neuroprotective effects of exercise may be mediated by exercise-induced increases in brain derived neurotrophic factor (BDNF), insulin-like growth factor-type I (IGF-1), vascular endothelial growth factor (VEGF) and homocysteine [15-23] thereby promoting structural and connectivity changes in brain areas important for memory and executive function, e.g., frontal and temporal lobe and hippocampus [24-27].

There is no conclusive evidence for exercise as treatment modality for PwD. Identifying the variables that moderate the relationship between cognition and physical function is needed to optimize exercise programs [28]. A few potential moderators have been identified. For example, the presence of the Apolipoprotein-E4 (ApoE4) allele, a risk factor for Alzeimer's Disease (AD)[29], may mediate the magnitude of exercise effects. Accumulation of neuronal and physiological damage in ApoE4-carriers may negate the beneficial effects of physical activity [30, 31]. Conversely, ApoE4-carriers may be more responsive to exercise [32], perhaps because lower functional levels at baseline [33-36] leave more room for improvement. In addition to ApoE4-carriership, exercise intensity may determine the magnitude of exercise effects. Exercise-induced changes in the aforementioned neurobiological factors may be dose-dependent, as evidenced by studies in rodents [37, 38] and humans [18, 39, 40]. Furthermore, exercising at moderate-to-vigorous intensities is recommended over lighter intensities for cardiovascular, muscular and neuromotor benefits in healthy young and old adults [41]. Whether this is true also for cognitive functions is undetermined [5].

In the current sample of PwD, we aimed to determine: 1) the feasibility of low- vs. high-

intensity combined aerobic and strength training, 2) the dose-response effects of low- and high-intensity combined aerobic and strength exercise on physical and cognitive functions, 3) if high- vs. low-intensity exercise has differential effects on physical and cognitive functions, and 4) whether ApoE4 moderates the effects of exercise. We hypothesized that: 1) a 6-month combined aerobic and strength training program with a low- vs. high-intensity phase would be feasible in our sample; 2) the exercise program would reduce the rate of decline in physical and cognitive function; 3) the beneficial effects would be greater after high- vs. low-intensity exercise, and 4) that ApoE4-carriership would moderate the effects of exercise on physical and cognitive functions.

Methods

Design

We assessed the effects of a 6-month combined aerobic and strength training program with a low (LI, week 1-12) and high (HI, week 13-24) intensity phase compared to a control program of matched attention in a randomized controlled study design. We performed blinded assessments of cognitive and physical functions at T0, T12 (after 12 weeks), and T24 (after 24 weeks). Brief (blinded) assessments of a selection of cognitive and physical functions were performed at T6 (after 6 weeks), T18 (after 18 weeks) and T36 (follow-up after 36 weeks). After 24 weeks, a saliva sample was taken to determine ApoE4-carriership. We included patients with mild-to-moderate dementia who attended daycare or resided in residential care facilities with open front door policies. A power analysis on our design using a small-to-medium effect size (ES), alpha=5%, power=80% and expected dropout of 25% resulted in a minimal sample size of 59 participants per group.

Participants

Between September 2015 and October 2017 participants were recruited from 13 health care locations that provided daycare or residential care for PwD. Health care staff selected potential participants based on instructions from the researchers. These instructions were that potential participants had to be able to walk with or without an assistive walking device, had to have sufficient ability to follow instructions, and had to be interested in participating in a study. The researchers provided the potential participants and their caregivers with oral and written

information and informed consent documents. Subsequently, participants were screened for eligibility by a trained research assistant. Participants were included if they met the following criteria: age ≥65 years; a physician-determined all-cause dementia diagnosis; able to complete the Timed Up & Go (TUG [42]) with or without assistive device; a Mini Mental State Examination (MMSE [43]) score >10 corresponding to mild to moderate dementia. Participants were excluded if they met one of the following criteria: wheelchair bound; presence of severe cardiovascular problems that limit physical activity or brain trauma, epilepsy, progressive or terminal disease and/or depression; history of alcoholism and/or Korsakoff's syndrome; severe visual or auditory problems; non-fluent in the Dutch language; mental incompetence without a legal guardian.

Procedures

The Ethical Committee of the University Medical Center Groningen approved the study (METc 2014/523). The Dutch Trial Registration number is NTR5035. We obtained oral and written informed consent from participants and their caregivers. The study was conducted in accordance with the Declaration of Helsinki (64th amendment).

Participants were randomly assigned to the combined aerobic and strength training intervention ('exercise') or control intervention ('control') with an allocation ratio 1:1. We stratified participants according to MMSE, gender and health care location, so that the number of exercise vs. control participants was approximately equally distributed per health care location.

Participants in each intervention were offered 72 individualized sessions (3/week for 24 weeks) of 30 minutes. This combination of combined walking and strength exercise, 3 sessions/week for 24 weeks previously showed the highest efficacy on physical and cognitive outcomes in PwD [11, 44]. Each session was supervised on a one-on-one basis by a trained research assistant who was assigned to the participant. Each research assistant kept a log of each session. The log was used to record heart rate and Rate of Perceived Exertion (RPE) during the session, activity specifics, participant satisfaction and noteworthy details.

Exercise intervention

Aerobic sessions

The aerobic sessions consisted of outdoor walking. If the weather did not allow for outdoor

walking or the participant rejected outdoor walking, walking was performed indoors.

Subjects in the exercise intervention exercised at LI for the first 12 weeks and at HI for the subsequent 12 weeks. The target intensity sessions was determined in correspondence with the American College of Sports Medicine (ACSM [45]) guidelines for 'low' and 'moderate to high' intensity exercise. The intensity of the aerobic sessions was monitored objectively every five minutes using a MIO Link Continuous Heart Rate Wrist Band. Subsequently, training intensity was determined objectively using the % of maximum heart rate (%HRmax, with HRmax=208-(0.7*age)) and subjectively with observer-determined RPE using a Borg scale. The Borg scale ranges from 6–20, with 6 corresponding to minimal intensity and 20 to maximal intensity. In the LI phase, the target RPE was 9-11 and target HR was 57-63%HRmax. In the HI phase, participants performed interval training with alternating four minutes peak performance at RPE 15-16 and 83-89%HRmax and three minutes active rest at RPE 13-14 and 71-77%HRmax. Walking intensity could be increased or decreased by adapting walking speed and the number of passive or active rests.

Strength sessions

Lower-limb strength exercises can help enhance walking ability and produce a stronger neuromotor stimulus [11]. Four lower-limb exercises were performed during the strength sessions in a fixed sequence: 1) knee extension while sitting, 2) plantar flexion (toe standing), 3) hip abduction (side leg lifts) and 4) hip extension (back leg lifts). A chair was used for support. Per session, all muscle contractions were either isometric, concentric or eccentric. We used only the target RPE to determine intensity because no significant increases in heart rate were expected.

The intensity of the strength sessions was determined subjectively with the observer-determined RPE. In the LI phase, the target RPE was 9-11. In the HI phase, the RPE was 13-16. Exercise intensity could be increased or decreased by adapting the number of sets and repetitions (Appendix 1). Ankle weights were added in the HI phase per 0.5 kg.

Control intervention

The control intervention consisted of flexibility exercises and recreational activities (matched attention). The flexibility exercises included upper and lower body exercises such as neck or shoulder rotation and stretching knee flexors and extensors. No weights were used. Additionally, recreational activities such as board games or social visits were performed depending on

the participants' preference.

Measurements

Medical information

We collected information on dementia diagnosis, comorbidities (Functional Comorbidity Index-18 (FCI-18 [46]), and medication use from medical files kept by each participants' general practitioner. Anticholinergic and sedative drug burden was represented by the Drug Burden Index (DBI [47]).

ApoE4 status

We used sterile buccal swabs to take saliva samples for APOE genotyping. Buccal samples were analyzed using the real-time Polymerase Chain Reaction method (PCR) [48]. This resulted in six different potential APOE genotypes (e2/e2, e2/e3, e2/e4, e3/e3, e3/e4, e4/e4).

Physical function

We used five physical function tests that are deemed suitable for PwD [49]. Appendix 2a describes these tests in more detail. The Six Minute Walk test (6MWT) [50] measures endurance. The Short Physical Performance Battery (SPPB) [51] assesses lower body strength and functional mobility. We measured habitual gait speed with the 6-meter walking speed test (6MWS). We used the FICSIT-4 [52] as static balance measure. We assessed lower body muscle strength with the Quadriso table (see Appendix 2a for details). The TUG measures functional mobility.

All tests were performed at T0, T12 and T24. 6MWS and leg strength were assessed at T6, T18 and T36 as well.

Cognitive function

We assessed cognitive function with neuropsychological tests that were previously used in PwD [49]. Appendix 2b describes these tests. Global cognition was assessed with the MMSE. We measured psychomotor speed with the Trail Making Test A (TMTA) [53]. The Digit Span Forward (DSFW) and Backward (DSBW) [54] measure verbal memory span and verbal working memory, respectively. The Visual Memory Span Forward and Backward (VMSFW and VMSBW) [54] are measures of respectively visual memory span and visual working memory. The STROOP test [55] is used to assess basic attentional processing and inhibitory control.

We used the Phonemic Fluency Test (Fluency) [56] as executive function measure.

All tests were performed at T0, T12 and T24. The STROOP test was also performed at T6, T18 and T36.

Statistical analyses

We used SPSS 25.0 (IBM: Armonk, NY) to compute means and standard deviations and to analyze the data with two-tailed significance set at p<0.05. Scores on the TMTA, STROOP interference, TUG and 6MWS were right-skewed and therefore natural-log transformed. We accounted for missing values on cognitive and physical variables at T0, T6, T12, T18, T24 and T36 with multiple imputation (9.2% of the cognitive variables missing (3.2% T0, 5.3% T6, 10.0% T12, 6.8% T18, 12.9% T24 20.3% T36) and 9.2% of the physical variables missing (2.4% T0, 13.0% T6, 8.9% T12, 10.1% T18, 11.1% T24 and 19.6% T36)); automatic model setting; 40 imputations; 100 iterations; done separately for physical vs. cognitive variables and exercise vs. control group). We performed intention-to-treat analyses on all individuals who completed ≥5 assessments (N=69, 39 exercise group). Group differences for physical and cognitive outcomes were assessed with analyses of covariance (ANCOVA) with continuous baseline variables as covariates.

To determine the magnitude of exercise effects, we calculated Cohen's d effect sizes (ESs) using the formula:

$$d = \frac{(post_{\text{exp}} - pre_{\text{exp}}) - (post_{\text{cont}} - pre_{\text{cont}})}{\sqrt{\frac{\frac{s^2_{\text{pre,exp}} * n_{\text{exp}} + s^2_{\text{pre,cont}} * n_{\text{cont}}}{n_{\text{exp}} + n_{\text{cont}}} + \frac{s^2_{\text{post,exp}} * n_{\text{exp}} + s^2_{\text{post,cont}} * n_{\text{cont}}}{n_{\text{exp}} + n_{\text{cont}}}}{2}}}$$

where 'post' represents T12 or T24 measurements; exp=exercise and cont=control group. Values of d=0.20, d =0.50, d=0.80 indicate small, medium and large effect sizes [57]. 95% Confidence Intervals (CI's) for d were calculated using the formula d±1.96*SE, with

$$SE = \sqrt{\left(\frac{n_{\text{exp}} + n_{\text{cont}} - 1}{n_{\text{exp}} + n_{\text{cont}} - 3}\right) * \left(\left(\frac{4}{n_{\text{exp}} + n_{\text{cont}}}\right) * \left(1 + \frac{d^2}{8}\right)\right)}$$ [58].

We considered an effect to be a dose-response effect with respect to intensity if the change from T12-T24 (HI phase) was higher or equal (as we expected that potential beneficial effects would become less pronounced over the course of the study) to the change from baseline-T12

(LI phase).

To examine ApoE4 as a potential moderator, we conducted a repeated-measures ANOVA with physical and cognitive outcome variables as dependent variable(s), time of measurement (baseline and T24) as within-subjects factor, and Group (exercise vs. control) and Carrier (ApoE4 carrier vs. non-carrier) as between-subjects factors. We considered ApoE4 to moderate the effects of exercise on physical or cognitive functions if there was a significant three-way Group*Carrier*Time interaction.

Results

Figure 1 shows the flowchart of the study. Of the 916 persons that were screened for eligibility, 91 were randomized (N=46 exercise vs. N=45 control; mean age=82.3±6.96; mean MMSE=20.2±4.40; 59 women). Of these 91 participants, 22 (24%) participants dropped out after allocation. There were no differences with respect to age, gender, level of education and baseline MMSE between participants who dropped out vs. participants who remained in the study (N=69). Figure 1 shows the time and reasons for drop-out.

Intention-to-treat analyses

The current analyses involve the participants who performed ≥5 assessments (N=69; N=39 exercise vs. N=30 control; mean MMSE=20.6±4.38; 43 women). Table 1 shows the baseline characteristics of this sample.

Appendix 3 presents training characteristics for the exercise (LI vs. HI phase) and control group. Overall attendance was ~60%. Attendance was not significantly different for the walking vs. strength sessions, LI vs. HI phase and exercise vs. control group. Participant satisfaction was generally high but lowered for the HI vs. LI walking sessions. For the HI vs. LI strength sessions, the RPE and number of repetitions were significantly higher with the added weight being ~0.71 kg (there were no added weights in the LI sessions). There was no loss of quality for the HI vs. LI strength exercises. The contrast between LI and HI walking was less pronounced. The total distance walked in 30 minutes was ~40m higher in the HI phase. However, mean and maximum heart rate were not significantly different between LI and HI walking sessions. Furthermore, there were no significant differences in maximum heart rate between participants with and without beta blockers. The mean HR of ~95 b/min-1 during LI and HI walking sessions falls within the low to low-moderate intensity

range and the maximum HR of ~135 b/min-1 during LI and HI walking sessions can be considered high intensity according to ACSM guidelines [45] (given the mean age=81.8, HRmax=208-0.7*81.8=~151).

The exercise intervention had a significant positive effect on 6MWS after 18 ($F(1,66)=5.12$, $p<0.05$) and 24 weeks (Table 2)(Figure 2b). The ES increased from d=0.04 at T12 to d=0.41 at T24 (Table 2). At follow-up 6MWS declined and was no longer significantly higher for the exercise vs. control group (Figure 2b). There were consistently small but non-significant effects of the exercise vs. control intervention on the other physical measures (mean d=0.18 for the LI phase and mean d=0.13 for the HI phase; Table 2, Figure 2c for leg strength).

There were no significant effects of the exercise vs. control intervention on any of the cognitive measures (mean d=-0.03 for the LI phase and mean d=-0.04 for the HI phase; Table 3, Figure 2a for all STROOP scores). Both the exercise and control participants stabilized over the course of the study.

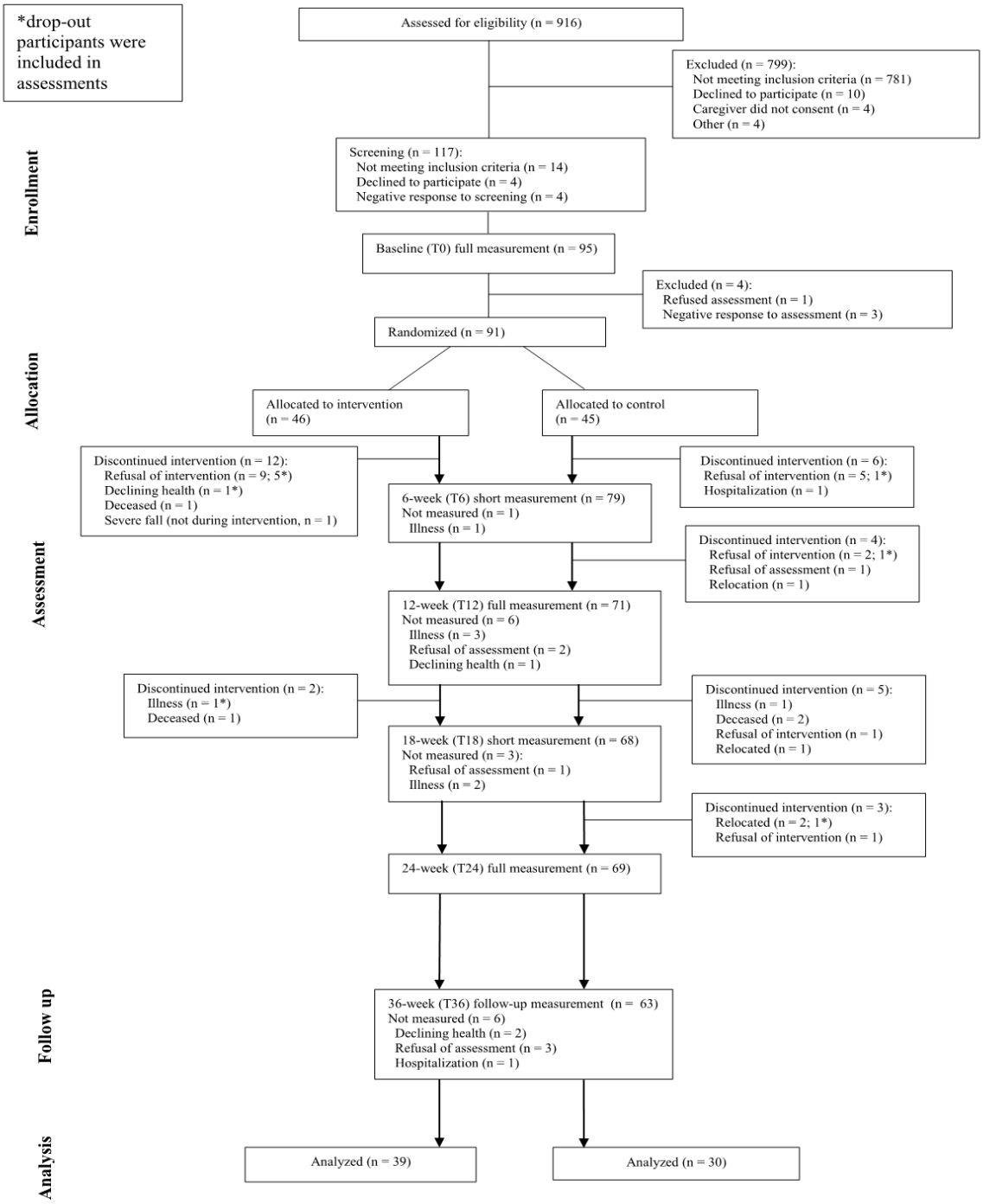

Figure 1. CONSORT flowchart.

Table 1. Sample characteristics at baseline.

Characteristic	Exercise (N=39)	Control (N=30)
Age (mean, SD)	81.7 (7.16)	82.1 (7.51)
Gender (N women, % total)	21 (53.8)	22 (73.3)
Level of education (N, % total)		
1 = primary education only	10 (25.6)	8 (26.7)
2 = secondary lower education	25 (64.1)	19 (63.3)
3 = secondary higher education	4 (10.3)	3 (10.0)
Use of walking aid at baseline (N, % total)	17 (43.6)	19 (63.3)
Dementia diagnosis according to medical file[a] (N, % total)		
1 = Alzheimer's Disease (AD)	14 (35.9)	7 (23.3)
2 = Vascular Dementia (VD)	3 (7.7)	1 (3.3)
3 = Mixed (AD+VD)	3 (7.7)	5 (16.7)
4 = Dementia with Lewy Bodies (DLB)	0 (0.0)	1 (3.3)
5 = Other/Unspecified[b]	11 (28.2)	12 (40.0)
MMSE[c] (mean, SD)	21.4 (3.94)	19.5 (4.77)
APOE[d] genotype (N, % total)		
Carrier (e3/e4 and e4/e4)	18 (46.2)	12 (40.0)
Non-carrier (e2/e2, e2/e3, e3/e3)	21 (53.8)	18 (60.0)
Number of medications used[e] (mean, SD)	5.2 (2.45)	5.1 (2.74)
Use of beta blockers (N, % total)	21 (53.8)	14 (46.7)
DBI[f] (mean, SD)	0.24 (0.38)	0.22 (0.31)
FCI[g] (mean, SD)	2.4 (1.66)	2.7 (1.96)
BMI[h] (mean, SD)	27.3 (3.53)	27.6 (3.71)

†significant at $p<0.1$. [a]N=12 missing; [b]Diagnosis of 'dementia' or 'dementia syndrome'; [c]Mini Mental State Examination; [d]Apolipoprotein E, within Carrier group N=2 homozygote in exercise group, N=1 homozygote in control group; [e]N=1 missing; [f]Drug Burden Index, N=4 missing; [g]Functional Comorbidity Index, N=9 missing; [h]Body Mass Index. [i]Physical Activity Scale for the Elderly, N=8 missing.

Figure 2a. STROOP scores for the intervention vs. control group

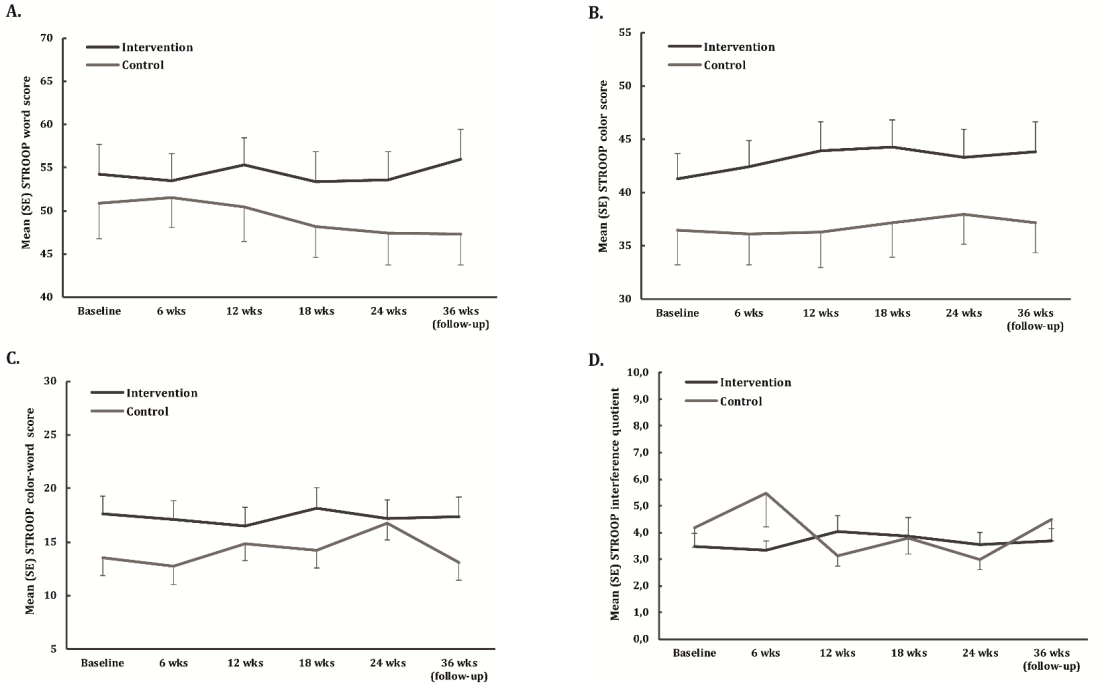

Figure 2b. 6 meter walking speed for the intervention vs. control group

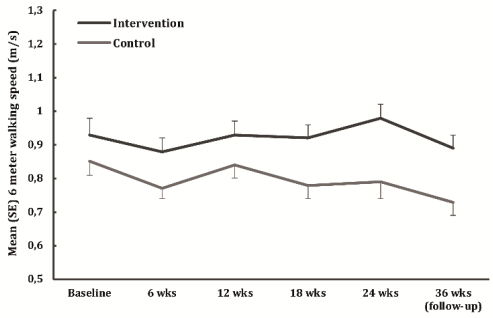

Figure 2c. Leg strength for the intervention vs. control group

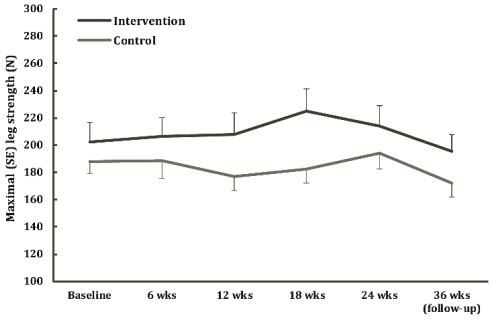

Figure 2. Scores on STROOP, 6 meter walking speed and leg strength for the intervention vs. control group.

Table 2. Descriptives, effect sizes and results of ANCOVA for physical test scores.

Test[a]	Group	Baseline	12 weeks	24 weeks	Effect size Baseline-12 weeks[b]	F(1,66)[c], p	Effect size Baseline-24 weeks[b]	F(1,66)[c], p
6MWT (m)	Exercise	278 (89.4)	280 (87.0)	289 (95.0)	0.18 [-0.30, 0.65]	2.73, p>0.05	0.08 [-0.40, 0.56]	1.36, p>0.05
	Control	234 (88.6)	222 (98.8)	238 (87.4)				
SPPB (score)	Exercise	8.75 (2.25)	9.19 (2.37)	8.96 (2.31)	0.28 [-0.20, 0.76]	3.27[c], p>0.05	0.16 [-0.32, 0.64]	2.46, p>0.05
	Control	7.77 (2.08)	7.58 (2.14)	7.61 (2.41)				
6MWS (m/s)	Exercise	0.93 (0.31)	0.93 (0.25)	0.98 (0.25)	0.04 [-0.44, 0.52]	1.46, p>0.05	0.41 [-0.07, 0.90]	12.83, p<0.001**
	Control	0.85 (0.22)	0.84 (0.22)	0.79 (0.27)				
FICSIT-4 (score)	Exercise	3.36 (1.06)	3.45 (1.19)	3.30 (1.31)	0.15 [-0.33, 0.63]	1.45, p>0.05	-0.15 [0.63, 0.33]	0.09, p>0.05
	Control	2.90 (1.40)	2.81 (1.24)	3.03 (1.35)				
TUG (s)	Exercise	14.4 (6.24)	13.6 (5.56)	14.1 (6.62)	0.23 [-0.26, 0.71]	2.35, p>0.05	0.17 [-0.31, 0.66]	1.43, p>0.05
	Control	17.3 (5.56)	17.8 (7.57)	18.0 (7.20)				
Leg strength (N)	Exercise	202 (91.4)	208 (98.4)	214 (95.8)	0.21 [-0.27, 0.69]	2.01, p>0.05	0.07 [-0.41, 0.55]	0.39, p>0.05
	Control	188 (51.4)	177 (58.5)	194 (67.0)				

Values are mean (SD). [a]6MWT = Six Meter Walk Test; SPPB = Short Physical Performance Battery; 6MWS = 6 meter walk speed; TUG = Timed Up&Go. [b]Cohen's d with 95% CI, positive effect sizes are in favor of exercise group. [c]ANCOVA with baseline as covariate, main effect of group (exercise vs. control). [c]ANCOVA with baseline as covariate and use of walking aid as factor, main effect of group (exercise vs. control). **Significant at p<0.001.

Table 3. Descriptives, effect sizes and results of ANCOVA for cognitive test scores.

Test[a]	Group	Baseline	12 weeks	24 weeks	Effect size[b] Baseline-12 weeks	F(1,66)[d], p	Effect size[b] Baseline-24 weeks	F(1,66)[d], p
MMSE (score)	Exercise	21.4 (3.94)	21.0 (4.38)	20.4 (4.77)	-0.05 [-0.53, 0.43]	0.11, p>0.05	-0.04 [-0.52, 0.44]	0.04, p>0.05
	Control	19.5 (4.77)	19.4 (5.64)	18.8 (5.88)				
TMTA (seconds)	Exercise	121 (64.2)	123 (63.7)	126 (65.3)	-0.03 [-0.51, 0.45]	0.51, p>0.05	-0.14 [-0.62, 0.34]	0.52, p>0.05
	Control	156 (65.2)	156 (61.1)	153 (56.6)				
STROOP word (#correct responses)	Exercise	54.3 (21.1)	55.3 (19.7)	53.5 (20.3)	0.07 [-0.41, 0.55]	0.64, p>0.05	0.13 [-0.35, 0.61]	1.35, p>0.05
	Control	50.9 (22.5)	50.5 (22.0)	47.4 (20.1)				
STROOP colour (#correct responses)	Exercise	41.3 (14.8)	43.9 (17.0)	43.3 (16.3)	0.17 [-0.31, 0.65]	1.93, p>0.05	0.03 [-0.45, 0.51]	0.47, p>0.05
	Control	36.4 (17.6)	36.3 (18.0)	38.0 (15.4)				
STROOP colour-word (#correct responses)	Exercise	17.6 (10.4)	16.5 (10.8)	17.2 (10.7)	-0.24 [-0.72, 0.24]	0.45, p>0.05	-0.37 [-0.85, 0.12]	0.61, p>0.05
	Control	13.5 (9.05)	14.9 (8.63)	16.8 (8.83)				
STROOP interference quotient	Exercise	3.46 (3.18)	4.04 (3.68)	3.56 (2.81)	-0.49 [-0.98, 0.00]	4.29, p=0.04*	-0.42 [-0.90, 0.07]	2.13, p>0.05
	Control	4.19 (3.99)	3.14 (2.21)	3.00 (2.21)				
DSFW (#correct responses)	Exercise	6.79 (1.77)	7.11 (2.14)	6.67 (1.80)	0.15 [-0.33, 0.63]	0.96, p>0.05	-0.13 [-0.61, 0.35]	0.40, p>0.05
	Control	6.53 (1.55)	6.58 (1.67)	6.64 (1.91)				
DSBW (#correct responses)	Exercise	4.00 (1.39)	4.00 (1.54)	4.01 (1.31)	-0.03 [-0.51, 0.45]	0.20, p>0.05	0.10 [-0.38, 0.58]	0.15, p>0.05
	Control	4.17 (1.32)	4.21 (1.48)	4.04 (1.60)				
VMSFW (#correct responses)	Exercise	5.78 (1.95)	5.50 (1.57)	5.23 (1.50)	0.04 [-0.43, 0.52]	2.01, p>0.05	-0.05 [-0.53, 0.43]	1.20, p>0.05
	Control	4.96 (1.80)	4.60 (1.82)	4.50 (2.05)				
VMSBW (#correct responses)	Exercise	4.31 (2.05)	4.23 (1.93)	4.56 (1.71)	0.14 [-0.34, 0.62]	0.71, p>0.05	0.33 [-0.16, 0.81]	2.92, p>0.05
	Control	4.30 (1.86)	3.94 (1.94)	3.93 (1.98)				
Fluency (#correct responses)	Exercise	18.9 (7.73)	18.3 (8.27)	21.6 (8.49)	-0.06 [-0.54, 0.42]	0.03, p>0.05	0.13 [-0.35, 0.61]	2.00, p>0.05
	Control	14.7 (9.39)	14.6 (9.95)	16.3 (9.52)				

Values are mean (SD). NTotal = 69; N=39 exercise vs. N=30 control. [a]MMSE = Mini-Mental State Examination; TMTA = Trail Making Test A; DSFW = Digit Span Forward; DSBW = Digit Span Backward; VMSFW = Visual Memory Span Forward; VMSBW = Visual Memory Span Backward; Fluency = Phonemic fluency. [b]Cohen's d with 95% CI, positive effect sizes are in favor of exercise group. [d]ANCOVA with baseline as covariate, main effect of group (exercise vs. control). *Significant at p<0.05.

ApoE4 moderation

ApoE4-carriers (n=30) were ~3 years younger than non-carriers (n=39) (non-significant difference) and used more beta blockers (66.7% of carriers and 38.5% of non-carries used beta blockers, $X^2(1)=5.40$, $p<0.05$). There were no other significant baseline differences. There was a trend-level significant three-way Time* Group* Carrier interaction for MMSE: non-carriers in the exercise group slightly improved on the MMSE after 24 weeks, whereas MMSE scores for carriers in the exercise group and both the carriers and the non-carriers in the control group declined ($F(1,65)=3.28$, $p=0.075$; Appendix 4a-4c, Figure 3). There were no significant three-way interactions for any of the other cognitive or physical variables (Appendix 4a-4c).

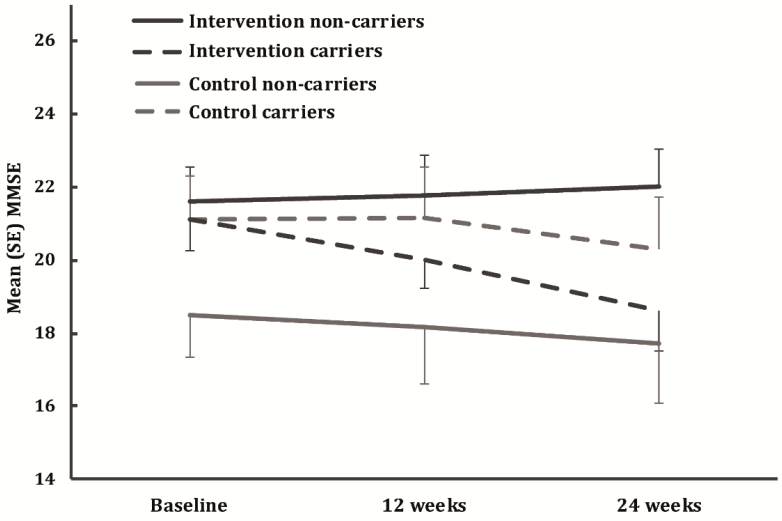

Figure 3. Three-way interaction (Time*Group*Carrier) for MMSE score.

Discussion

Summary of results

This is the first assessor-blinded RCT investigating the effects of LI vs. HI combined aerobic and strength exercise in PwD. Gait speed significantly improved for the exercise vs. control group after 24 weeks (d=0.41, p<0.05) but declined at follow-up. We found small but non-significant effects of exercise on the other physical functions. There were no differences between the LI (mean d=0.18) and HI (mean d=0.13) phase. There were no effects of exercise on cognitive functions and no differences between the LI (mean d=-0.03) and HI (mean d=-0.04) phase. Global cognition (MMSE) improved for ApoE4 non-carriers in the exercise group and declined for the other groups (trend-level significant).

Feasibility of the exercise program

This exercise program was feasible in this sample of PwD. The mean attendance rate was ~60% in the LI and HI phase. All exercise participants were able to perform the strength exercises with and without weights. There were no serious study-related adverse events. Notwithstanding the individual supervision, the mean attendance rate was lower than what is considered necessary for functional improvements (i.e. ≥3 performed sessions per week) [41]. However, higher attendance was not predictive of better physical or cognitive effects (additional analyses, data not shown).

We aimed to contrast LI with HI exercise. LI walking consisted of slow walking with passive rests whereas participants walked in HI intervals with active rests during the HI walking sessions. During the strength sessions participants performed exercises without (LI) vs. with (HI) ankle weights, and we aimed to increase the number of repetitions during the HI phase. Overall our results confirm the contrast between LI and HI exercise. However, this contrast was more pronounced for the LI vs. HI strength exercises than for LI vs. HI walking. With respect to walking, the RPE was significantly higher in the HI phase but heart rate was not. We are unsure if heart rate is a reliable indicator of exercise intensity in PwD. All types of dementia are associated with dysfunction of the autonomic nervous system including heart rate variability [59]. This may influence the heart rate response to exercise in PwD. Future studies are needed to investigate whether there are differences in heart rate response to exercise in PwD vs. healthy older adults.

We had selective drop-out in our sample as our baseline sample (N=91) showed no

differences in baseline characteristics (age, gender, education, MMSE, endurance capacity and use of walking aid; data not shown) whereas in our analyzed sample (N=69) exercise participants had higher levels of physical and cognitive functions at baseline compared with control participants. Despite starting with LI exercise, lower functioning individuals were more likely to drop-out of the exercise group often within the first weeks of the study. This could perhaps have been prevented with a more gradual increase in session duration or frequency. Conversely, higher functioning individuals were more likely to drop-out of the control group. This could perhaps have been prevented with more challenging control activities.

Effects of exercise on physical function

Gait speed significantly improved with ~5% after 24 weeks. Gait speed is an important clinical measure in older adults because it is associated with rate of cognitive decline [60], vulnerability to adverse events [61] and survival [62]. The change in gait speed for participants in the exercise group between baseline and T24 was ~0.05 m/s which is considered functionally meaningful [63]. It is unlikely that the effects of exercise on gait speed were random as gait speed improved in respectively 38% vs. 13% of exercise vs. control participants (change ≥0.05 m/s). The finding that gait speed improved more in the HI vs. the LI phase may be indicative of a dose-response effect for intensity. The LI vs. HI contrast was most pronounced for the strength sessions. These results attest to a relationship between gait speed improvements and strength improvements [64]. A lack of significant (dose-response) improvements in leg strength may have resulted from our assessment method: PwD may be hesitant to generate maximum force either in fear of pain or injury, or lack of motivation. Also, PwD may have trouble comprehending the test instructions. Exercise did not provide a protective effect against gait speed losses when exercise was withdrawn, as indicated by a decline in gait speed after detraining (at follow-up). Thus, our results support the recommendation of continuous physical exercise for PwD.

There were consistently small, non-significant beneficial effects of exercise on physical function. This complements earlier evidence of combined exercise to be related to better endurance, walking efficiency, mobility, muscle strength and balance in PwD ([11, 44, 65, 66]. Exercise interventions specifically in daycare or residential care settings have generated conflicting results [67-70]. Perhaps, exercise effects are lower for PwD in daycare or residential care due to stressors related to disease progression, disease awareness, caregiver burden, and

irregularity of daily life. Future studies could consider the impact of living environment on the effects of exercise in PwD. Our control group stabilized, which could attest to a confounding effect of daycare or residential care activities. However, this is unlikely as we found a drop in level of physical activity after the intervention (additional measurements using structured questionnaires with formal and informal caregivers, data not shown). Perhaps, the cognitive stimulation of the control activities afforded physical function benefits which strengthens the evidence for reverse causality in the relationship between physical and cognitive function that was previously found for gait speed [71]. Furthermore, the flexibility exercises of the control group require coordination which may have afforded cognitive benefits.

Effects of exercise on cognitive function

We found no effects of exercise vs. control activities on cognitive function and no differences between LI (d=-0.03) and HI (d=-0.04) exercise. Earlier evidence for the effects of exercise on cognition is conflicted for PwD in nursing homes [10, 11, 13, 65, 72] as well as community settings [14, 73-76]. Studies specifically in daycare or residential care settings are scarce. One RCT in PwD attending daycare showed that aerobic training had favorable effects on psychomotor speed only [77]. Altogether, there is a lack of convincing evidence for the efficacy of exercise for cognition in PwD. As mentioned previously for physical function, dementia-related factors such as disease progression, environmental factors and caregiver burden may confound the effects of exercise on cognition in PwD. Alternatively, a lack of convincing effects of exercise on cognition may indicate that exercise only does not sufficiently stimulate cognition in PwD. Diversity in symptoms and disease etiology may require diverse interventions and exercise could be one option for PwD in addition to cognitive training, social stimulation and sensory enrichment [78]. Recent conceptual models suggest that it may be necessary to perform cognitive and motor tasks in combination and concurrently to increase efficacy of exercise interventions [79]. Additionally, a more individualized approach as opposed to a standardized program may be necessary for optimal results [80]. Contrary to clinical expectations, both the exercise and control participants stabilized over 24 weeks which attests to beneficial effects of attention and control activities on cognition. Controls participated in recreational activities which may stimulate aspects of cognition in PwD [81]. Indeed, the average MMSE decline of -0.7 in the control group (Table 3) is lower than the ~1.2-4 point decline that was previously found in comparable samples of PwD [75, 82]. To conclude, for PwD performing activities of any kind may be beneficial for cognition.

Contrary to our expectations, there were no differential effects of the LI and HI phase. We expected a dose-response relationship for intensity between exercise and cognition because higher intensity exercise is related to better fitness parameters [44] which could translate to changes in cognitive function. In a previous meta-analysis, we could not relate exercise intensity to changes in cognitive function in older adults with cognitive impairments [5], but studies that compared exercise intensities among randomized subjects were lacking. This is the first such study in patients with dementia. With this study, we cannot provide evidence that the effects of exercise on cognition can be enhanced by increasing exercise intensity. It should be noted that the distinction LI-HI could be made for strength training, but not convincing for walking. Future studies could investigate whether exercise intensity is related to changes in physiological parameters that may underlie cognitive changes in patients with dementia.

ApoE4 moderation

We found that MMSE improved slightly for non-carriers in the exercise group and decreased for all other groups. This finding complements post-hoc findings from the FAB study that showed a significantly better change in global cognition (ADAS-COG) in ApoE4 non-carriers in the exercise group compared to others [83]. A higher rate of clinical decline and atrophy in ApoE4 carriers vs. non-carriers [84] may negate the beneficial effects of physical activity. However, we urge caution when interpreting this result as we found it for one test only and it was not significant. Thus, at this time we cannot conclude that ApoE4-carriership is an important moderator in exercise studies with PwD.

Strengths and limitations

There were several strengths to this study. We selected intervention characteristics (i.e., combined walking and strength exercise, 3 sessions/week for 24 weeks) that previously showed the highest efficacy on physical and cognitive outcomes in PwD [11, 44]. As compared to a three-group design with LI exercise vs. HI exercise vs. control, our current two-group exercise vs. control design ensured that participants could gradually build up exercise intensity and heterogeneity remained as low as possible. Furthermore, we conducted our study in a practical health care setting to strengthen the ecological validity of our findings. Last, we opted for individually supervised sessions in a carefully controlled design.

Several limitations warrant caution in the interpretation of our results. The current

results have to be interpreted in light of limited sample size. Also, the study was set in fall/winter for logistical reasons, and we cannot rule out seasonal influences on dementia decline. Unfortunately, we have no information on the neurobiological factors (i.e., changes in IGF-1, VEGF, BDNF levels) hypothesized to underlie beneficial effect of exercise on brain health. Such information is important because Alzheimer's Disease (AD) has been associated with lower serum levels of IGF-1 [85] and BDNF [86]. Although lower levels in these neurobiological factors could leave more room for improvement, it is also possible that the neurobiological system is less responsive in PwD [87,88]. It is left to future exercise studies to account for changes in such neurobiological factors in PwD. Last, the cognitive tests that we employed are often used but not all psychometrically evaluated in PwD [49], and dementia-related fluctuations in cognitive function may lower the reliability of cognitive tests in general. Future studies are needed to validate commonly used neuropsychological tests and adapt tests to suit the needs of PwD.

Conclusions

Exercise was superior to control activities for better gait speed. This is an important result because gait speed has high clinical relevance in older adults. There was a dose-response relationship for intensity between exercise and gait speed improvements, which may have been fueled by strength improvements in the HI phase. We found small but non-significant effects of exercise on the other physical functions. Exercise was not superior to control activities for cognition in PwD. With gait speed as exception, we found no evidence that higher intensity exercise afforded more physical or cognitive benefits. Altogether, our results are not in contrast with the recommendation for physical activity over control activities for PwD, preferably at higher intensities, in accordance with ACSM's guidelines [45].

Declarations

Ethics approval and consent to participate

The Ethical Committee of the University Medical Center Groningen approved the study (METc 2014/523). We obtained oral and written informed consent from participants and their caregivers. The study was conducted in accordance with the Declaration of Helsinki (64th amendment).

Consent for publication

Consent for publication not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception MvH, TH, EvdZ, ES; design LS, MvH, TH; data acquisition LS; analysis and interpretation LS, MvH, TH; drafting of manuscript LS, MvH, TH; revising the manuscript all authors.

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Appendices

Appendix 1. Adaptation of sets and repetitions during strength sessions.

Each participant started every exercise with 2 sets of 6 repetitions without added weights. When the participant had yet to reach the target intensity, another 2 repetitions were added to a maximum of 12 repetitions. Further increasing of intensity was done by adding an extra set, with a total of 3 sets of 12 repetitions per exercise. If it was necessary to decrease intensity, 2 repetitions were subtracted to a minimum of 2 sets of 2 repetitions per exercise. The participant started the strength session thereafter with the number of sets and repetitions that he/she successfully completed during the previous session. In the HI phase every participant started with 2 sets of 6 repetitions with an ankle weight of 0.5 kg. The method of increasing and decreasing the intensity was equivalent to the LI phase, but after 3 sets of 12 repetitions the participants started at 2 sets of 8 repetitions with another 0.5 kg ankle weight and so forth.

Appendix 2a. Description of the physical function tests.

The Six-Meter Walk Test (6MWT) measures endurance. Participants walk as many rounds as possible of two cones set 10m apart within 6 minutes. The total distance walked is recorded. The SPPB assesses lower body strength and functional mobility. The Short Physical Performance Battery (SPPB) includes standing balance (feet together, semi-tandem, tandem, one-leg stance), habitual 6-meter walking speed (6MWS, m/s) and 5 times chair stand (5STS). A score of 0 (lowest) to 4 (highest) is given per condition so that the total score of the SPPB lies between 0-12. The FICSIT-4 measures static balance (feet together, semi-tandem, tandem, one-leg stance). Participants have to hold each stance for 10s. Scores range between 0 (no stances performed $\geq$10s) to 5 (all stances performed $\geq$10s). We assessed lower body muscle strength with the Quadriso table, which we based on the Quadrisotester of Verkerke et al. [1]. The Quadriso table was found to be a feasible, reliable and valid measure of maximal voluntary isometric force of the quadriceps muscle (unpublished data). Participants are instructed to sit on a table with a force measuring device above the ankle. Participants have to generate maximal force for 3s. Three trials are performed for each leg and the maximum force in Newton (N) is recorded. Last, the TUG measures functional mobility. Participants are instructed to rise from a chair, walk 3 meters and sit down again. We used the fastest time of two trials as outcome.

References

1. Verkerke GJ, Lemmink KA, Slagers AJ, Westhoff MH, van Riet GA, Rakhorst G. Precision, comfort and mechanical performance of the Quadriso-tester, a quadriceps force measuring device. Med Biol Eng Comput 2003, 41:283-289.

Appendix 2b. Description of the cognitive function tests.

Global cognition was assessed with the Mini Mental State Examination. Scores range from 0-30 with 30 being the best performance. The Trail Making Test A (TMTA) measures psychomotor speed. Participants have to sequentially connect numbers 1-25. We recorded the time to complete the test (s) with 240s as cut-off score. The Digit Span Forward measures verbal memory span. Participants repeat a sequence of digits of increasing length. In the Digit Span Backward, a measure of verbal working memory, participants have to repeat the sequences of digits in reverse order. For both tests, the number of correct responses is used as outcome measure. The Visual Memory Span Forward and Backward (VMSFW and VMSBW) are measures of respectively visual memory span and visual working memory. In the VMSFW, participants have to tap a block sequence of increasing length. In the VMSBW, the sequence of blocks has to be tapped in reverse order. The number of correct responses is recorded in both conditions. The STROOP test is used to assess basic attentional processing and inhibitory control. In condition I, participants read the names of four colors (blue, red, yellow, green). In condition II participants are asked to name the four colors. Condition III is the interference condition, in which participants have to name the color of words that are printed in incongruent colors (i.e. the word 'blue' printed in red ink). In all conditions, we recorded the number of correct responses in 45s. An interference score is obtained by dividing the scores on condition II by condition III. Larger scores represent more interference. The Phonemic Fluency Test (Fluency) was used as executive function measure. Participants need to name as many words as possible that start with a given letter within 1 minute. The number of correct responses in three attempts is recorded.

Appendix 3. Training characteristics for the exercise and control group.

Characteristic	Exercise (N=39)						Control (N=30)	Exercise vs. control
	Walking			Strength				
	LI phase[a]	HI phase[a]	Difference HI-LI	LI phase[a]	HI phase[a]	Difference HI-LI		
Adherence (% performed sessions/offered sessions, mean, SD)	57.3 (23.4)	58.0 (29.2)	0.71 (14.2)	62.4 (23.1)	65.1 (29.8)	2.70 (20.5)	69.5 (18.5)	*U*=475[h]
Heart rate, beats/min^{-1}[b] (mean, SD)	94.7 (12.1)	96.2 (12.4)	1.41 (8.51)	n\a	n\a	n\a	74.6 (11.4)	t(60)=-7.18**[i]
Heart rate difference after-before session, beats/min^{-1}[b] (mean, SD)	18.7 (12.4)	19.0 (11.8)	0.32 (15.2)	n\a	n\a	n\a	-0.52 (2.92)	*U*=986**[i]
Maximum heart rate, beats/min^{-1}[c] (SD)	132.9 (21.2)	137.8 (19.8)	4.88 (19.2)	n/a	n/a	n/a	n/a	n/a
RPE[d] (mean, SD)	9.10 (1.25)	12.2 (1.73)	3.09 (1.58)**	8.95 (1.35)	12.6 (2.15)	3.61 (1.99)**	7.03 (1.16)	*U*=992**[j]
RPE difference after-before session[e] (mean, SD)	2.78 (1.44)	6.03 (2.49)	3.26 (2.12)**	n\a	n\a	n\a	0.06 (0.28)	*U*=1134**[k]
Distance walked, km[f] (mean, SD)	1.30 (0.55)	1.34 (0.62)	0.04 (0.28)	n\a	n\a	n\a	n\a	n\a
Number of repetitions[g] (mean, SD)	n\a	n\a	n\a	78.5 (46.6)	107.6 (75.9)	29.1 (63.5)**	n\a	n\a
Added weight, kg[g] (mean, SD)	n\a	n\a	n\a	n\a	0.71 (0.43)	n\a	n\a	n\a
Quality[g] (mean, SD)	n\a	n\a	n\a	2.55 (0.41)	2.58 (0.50)	0.03 (0.44)	n\a	n\a
Participant satisfaction[d] (mean, SD)	1.82 (0.23)	1.63 (0.37)	-0.19 (0.28)**	1.80 (0.23)	1.71 (0.41)	-0.09 (0.35)	1.83 (0.25)	*U*=334*[h]

[a]LI = low intensity phase; HI = high intensity phase. n\a = not applicable. *p<0.05; **p<0.01; †p<0.1. [b]N=1 upper outlier removed, N=5 missing for LI and/or HI walking, N=1 missing for control; [c]N=2 upper outlier removed, N=5 missing for LI and/or HI walking, [d]N=5 missing for LI and/or HI walking, N=4 missing for LI and/or HI strength; [e]N=5 missing for LI and/or HI walking; [f]N=6 missing for exercise group; [g]N=4 missing for LI and/or HI strength. [h]Average total exercise vs. control; [i]average walking LI/HI vs. control; [j]average walking LI + strength LI vs. control; [k]walking LI vs. control.

Appendix 4a. Means and standard deviations for the imputed cognitive test scores for ApoE4 carriers vs. non-carriers.

		Exercise			ES[c] [95% CI]	Control			ES[c] [95% CI]
Test[a]	**Group**	**Baseline**	**12 weeks**	**24 weeks**	**Baseline – 24 wks**	**Baseline**	**12 weeks**	**24 weeks**	**Baseline – 24 wks**
MMSE (score)	Carriers	21.1 (3.61)	20.0 (3.31)	18.6 (4.54)	0.66 [0.00, 1.32]	21.1 (4.19)	21.2 (4.69)	20.3 (4.94)	-0.01 [-0.75, 0.73]
	Non-carriers	21.6 (4.28)	21.8 (5.07)	22.0 (4.50)		18.5 (4.96)	18.2 (6.01)	17.7 (6.33)	
TMTA (seconds)	Carriers	127 (62.2)	143 (62.7)	139 (60.1)	0.19 [-0.46, 0.84]	150 (72.4)	148 (57.8)	142 (54.8)	-0.14 [-0.88, 0.61]
	Non-carriers	116 (66.9)	105 (60.8)	116 (69.1)		160 (61.8)	161 (64.3)	160 (58.0)	
STROOP word (#correct	Carriers	48.3 (22.5)	52.0 (17.0)	46.4 (17.7)	0.11 [-0.54, 0.75]	56.7 (20.6)	55.3 (18.8)	51.2 (21.4)	0.16 [-0.58, 0.90]
responses)	Non-carriers	59.4 (18.9)	58.2 (21.6)	59.6 (20.8)		47.0 (23.5)	47.3 (23.9)	44.9 (19.3)	
STROOP colour	Carriers	36.9 (13.8)	38.2 (15.5)	37.3 (14.3)	0.21 [-0.44, 0.85]	37.9 (17.5)	39.5 (18.1)	41.4 (15.1)	-0.19 [-0.94, 0.55]
(#correct responses)	Non-carriers	45.0 (14.9)	48.8 (17.1)	48.4 (16.6)		35.4 (18.1)	34.1 (18.2)	35.7 (15.6)	
STROOP colour-word	Carriers	18.2 (9.71)	14.8 (8.91)	13.7 (8.64)	0.73 [0.06, 1.40]	14.9 (8.79)	15.5 (9.36)	18.0 (8.24)	0.02 [-0.72, 0.76]
(#correct responses)	Non-carriers	17.1 (11.1)	18.0 (12.2)	20.2 (11.5)		12.6 (9.34)	14.4 (8.32)	15.9 (9.33)	
STROOP interference	Carriers	3.31 (3.82)	4.09 (4.07)	4.48 (3.78)	0.66 [0.00, 1.33]	3.43 (2.81)	3.18 (1.91)	2.79 (1.49)	0.28 [-0.48, 1.04]
quotient[b]	Non-carriers	3.58 (2.61)	4.00 (3.35)	2.78 (1.10)		4.72 (4.70)	3.11 (2.47)	3.16 (2.60)	
DSFW	Carriers	6.67 (1.88)	6.80 (2.04)	6.56 (1.77)	-0.02 [-0.66, 0.63]	6.83 (1.53)	6.92 (1.78)	6.83 (1.75)	0.10 [-0.64, 0.84]
(#correct responses)	Non-carriers	6.90 (1.70)	7.38 (2.23)	6.76 (1.88)		6.33 (1.57)	6.36 (1.59)	6.51 (2.04)	
DSBW	Carriers	3.94 (1.51)	3.78 (1.34)	3.79 (1.34)	0.21 [-0.43, 0.86]	4.08 (1.38)	4.50 (1.38)	3.92 (1.73)	0.03 [-0.71, 0.78]
(#correct responses)	Non-carriers	4.05 (1.32)	4.19 (1.71)	4.19 (1.30)		4.23 (1.32)	4.01 (1.55)	4.12 (1.54)	
VMSFW	Carriers	5.70 (2.18)	5.25 (1.54)	5.21 (1.67)	-0.06 [-0.71, 0.58]	5.17 (2.12)	4.75 (2.26)	4.33 (1.97)	0.32 [-0.43, 1.06]
(#correct responses)	Non-carriers	5.85 (1.78)	5.71 (1.62)	5.25 (1.41)		4.83 (1.59)	4.51 (1.52)	4.61 (2.14)	
VMSBW	Carriers	3.72 (1.96)	3.94 (1.99)	4.34 (1.71)	-0.36 [-1.01, 0.29]	4.75 (1.98)	4.67 (2.15)	4.08 (2.15)	0.26 [-0.49, 1.00]
(#correct responses)	Non-carriers	4.81 (2.04)	4.49 (1.87)	4.75 (1.74)		3.99 (1.75)	3.46 (1.68)	3.82 (1.90)	
Fluency	Carriers	18.4 (8.76)	18.1 (8.60)	21.6 (8.31)	-0.11 [-0.76, 0.53]	16.1 (8.19)	16.8 (10.2)	19.1 (11.6)	-0.26 [-1.00, 0.49]
(#correct responses)	Non-carriers	19.3 (6.93)	18.4 (8.20)	21.6 (8.86)		13.8 (10.2)	13.2 (9.79)	14.4 (7.67)	

ApoE4 = Apolipoprotein e4. NTotal=69; Exercise group: N=18 carriers vs. N=21 non-carriers; Control group: N=12 carriers vs. N=18 non-carriers. [a]MMSE = Mini-Mental State Examination; TMTA = Trail Making Test A; DSFW = Digit Span Forward; DSBW = Digit Span Backward; VMSFW = Visual Memory Span Forward; VMSBW = Visual Memory Span Backward; Fluency = Phonemic fluency. [b]Colour/colour-word score; N=1 missing for control. [c]ES = Effect size; positive effect sizes are in favor of non-carriers. There were no significant baseline differences (all p>0.05).

Appendix 4b. Means and standard deviations for the imputed physical test scores for ApoE4 carriers vs. non-carriers.

	Group	Exercise			ES[b] [95% CI]	Control			ES[b] [95% CI]
Test[a]		Baseline	12 weeks	24 weeks	Baseline – 24 wks	Baseline	12 weeks	24 weeks	Baseline – 24 wks
6MWT (m)	Carriers	292 (94.1)	288 (91.6)	296 (102)	0.15 [-0.49, 0.80]	257 (93.9)	221 (92.2)	249 (89.6)	0.24 [-0.51, 0.98]
	Non-carriers	264 (85.3)	274 (84.6)	282 (91.0)		219 (84.0)	224 (106)	231 (87.6)	
SPPB (score)	Carriers	8.45 (2.24)	9.12 (2.34)	9.06 (1.99)	-0.33 [-0.98, 0.32]	7.75 (2.34)	7.58 (2.06)	7.67 (1.56)	-0.06 [-0.80, 0.69]
	Non-carriers	9.01 (2.21)	9.25 (2.48)	8.87 (2.64)		7.78 (1.99)	7.58 (2.24)	7.57 (2.86)	
6MWS (m/s)	Carriers	0.97 (0.30)	0.95 (0.27)	1.02 (0.29)	-0.02 [-0.67, 0.62]	0.88 (0.19)	0.85 (0.23)	0.84 (0.21)	0.19 [-0.57, 0.94]
	Non-carriers	0.90 (0.33)	0.91 (0.25)	0.95 (0.23)		0.84 (0.21)	0.83 (0.25)	0.76 (0.30)	
FICSIT-4 (score)	Carriers	3.31 (1.27)	3.50 (1.06)	3.36 (1.41)	-0.20 [-0.84, 0.45]	3.13 (1.57)	2.92 (1.36)	3.08 (1.00)	0.21 [-0.55, 0.97]
	Non-carriers	3.41 (0.92)	3.41 (1.33)	3.22 (1.29)		2.74 (1.26)	2.73 (1.20)	2.99 (1.61)	
TUG (s)	Carriers	13.0 (5.49)	13.2 (5.58)	13.3 (6.33)	0.20 [-0.45, 0.84]	15.4 (5.31)	15.6 (5.47)	15.9 (5.57)	-0.06 [-0.83, 0.71]
	Non-carriers	15.7 (6.72)	13.9 (5.64)	14.7 (6.94)		18.5 (5.52)	19.3 (8.53)	19.3 (7.92)	
Leg strength (N)	Carriers	181 (80.1)	197 (80.4)	206 (82.9)	-0.25 [-0.90, 0.40]	184 (64.4)	199 (64.2)	208 (86.1)	-0.50 [-1.25, 0.25]
	Non-carriers	220 (98.5)	217 (113)	221 (107)		191 (42.5)	163 (51.1)	185 (51.3)	

ApoE4 = Apolipoprotein e4. NTotal=69; Exercise group: N=18 carriers vs. N=21 non-carriers; Control group: N=12 carriers vs. N=18 non-carriers.. [a]6MWT = Six Meter Walk Test; SPPB = Short Physical Performance Battery; 6MWS = 6 meter walk speed; TUG = Timed Up&Go. [b]ES = Effect size; positive effect sizes are in favor of non-carriers. There were no significant baseline differences (all p>0.05).

Appendix 4c. Three-way time x group x ApoE4 carriership analyses for cognitive and physical functions.

Domain	Test[a]	F(1,65)[c], p
Cognition	MMSE (score)	3.28, p=0.075†
	TMTA (seconds)	0.69, p>0.05
	STROOP word (#correct responses)	0.03, p>0.05
	STROOP colour (#correct responses)	1.28, p>0.05
	STROOP colour-word (#correct responses)	2.56, p>0.05
	STROOP interference quotient[b]	0.87, p>0.05
	DSFW (#correct responses)	0.21, p>0.05
	DSBW (#correct responses)	0.24, p>0.05
	VMSFW (#correct responses)	0.65, p>0.05
	VMSBW (#correct responses)	1.70, p>0.05
	Fluency (#correct responses)	0.23, p>0.05
Physical function	6MWT (m)	0.04, p>0.05
	SPPB (score)	0.44, p>0.05
	6MWS (m/s)	1.02, p>0.05
	FICSIT-4 (score)	0.93, p>0.05
	TUG (s)	0.29, p>0.05
	Leg strength (N)	0.06, p>0.05

[a]MMSE = Mini-Mental State Examination; TMTA = Trail Making Test A; DSFW = Digit Span Forward; DSBW = Digit Span Backward; VMSFW = Visual Memory Span Forward; VMSBW = Visual Memory Span Backward; Fluency = Phonemic fluency; 6MWT = Six Meter Walk Test; SPPB = Short Physical Performance Battery; 6MWS = 6 meter walk speed; TUG = Timed Up&Go. [b]Colour/colour-word score. [c]Repeated Measures ANOVA with time (pre- vs. postteset) as within-subjects factor, and group (exercise vs. control) and ApoE4 carrier (carrier vs. non-carrier) as between-subjects factors; three-way interaction. †significant at p<0.1.

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